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Does Sildenafil Improve Physical Function in Patients With Idiopathic Pulmonary Fibrosis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not sildenafil improves physical function in patients with idiopathic pulmonary fibrosis.

Study Design: Review of 3 primary research studies published in the English language between 2007 and 2010.

Data Sources: Two randomized, double blind, placebo controlled clinical trials, and one open label study analyzing the effect of sildenafil on patients with idiopathic pulmonary fibrosis were found using PubMed.

Outcome Measured: The primary tool used to assess physical function in patients with idiopathic pulmonary fibrosis, when treated with sildenafil, was a 6-minute walk distance. Distances were compared before and after treatment to assess for efficacy.

Results: Two randomized controlled trials showed sildenafil was not effective at increasing physical function, and one open label study showed improved physical function. The study by the idiopathic pulmonary fibrosis clinical research network showed no significant difference between the sildenafil and control groups at 12 weeks. The study by Jackson et al. found sildenafil did not improve physical function in patients with idiopathic pulmonary fibrosis. The open label study by Collard et al. showed that when patients with idiopathic pulmonary fibrosis were given sildenafil, the majority showed improved physical function.

Conclusions: Based on the analysis of the two randomized controlled trials, sildenafil does not improve physical function. The open label study did show improved physical function in the majority of patients with idiopathic pulmonary fibrosis, but this is weak correlation at best, since it is neither randomized nor controlled.

Key Words: Sildenafil, idiopathic pulmonary fibrosis

Introduction:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, form of interstitial lung disease of unknown origin that is characterized by heterogeneous fibroblast proliferation and poor prognosis.[2] Almost one half, 46%, of patients with IPF who are awaiting lung transplant have pulmonary hypertension (pulmonary artery pressure > 25 mmHg) on right heart catheterization.[3] This signifies an impairment leading to decreased resting and exercise induced levels of nitric oxide. Nitric oxide is a potent pulmonary vasodilator; so its reduction is associated with impaired gas exchange.[2] Sildenafil stabilizes cGMP, an intermediary in the nitric oxide pathway, thereby increasing nitric oxide in arterial wall smooth muscle. This paper evaluates two double blind, randomized, controlled trials comparing the efficacy of sildenafil as a medication for improving physical function in patients with IPF; and one open label study evaluating whether patients with IPF showed improved physical function with the use of sildenafil or not.

This disease affects about 128,100 people in the United States, with about 48,000 new cases diagnosed annually, and about 40,000 deaths each year.[4] In patients aged older than 55 years, total direct costs for patients with idiopathic pulmonary fibrosis are $26,378 per person-year.[5] Also, a cohort study showed that outpatient visit rate in individuals with IPF was about two times as high those in a the control group, 28 visits/person/year.[5]

IPF is the most common form of interstitial lung disease, the cause of which remains unknown.[1,2] It is rapidly fatal with respiratory failure and death just 5 years after the onset of symptoms. Symptoms include dyspnea, unexplained weight loss, digital clubbing, and chronic dry cough. It presents in a pattern consistent with usual interstitial pneumonia (UIP), in which

progressive interstitial scarring in the periphery and at the bases of the lungs is apparent radiologically.

The treatments for IPF are not FDA approved. Patients are usually prescribed "triple combination therapy" which consists of systemic corticosteroids, azathioprine, an immunomodulator, and NAC, an antioxidant. Supplemental oxygen assists to decrease the work of breathing. Pulmonary rehabilitation is a multidisciplinary approach to increasing exercise tolerance, quality of life, and disease knowledge in patients with chronic lung disease. IPF is one of the leading indications for lung transplantation; however wait lists can be the limiting factor here, where time is of the essence.

There is no known cure for IPF, the listed treatments allow for increased quality of life as the disease progresses. Unfortunately, the current pharmacologic therapies have not definitively increased survival or quality of life. Many of the patients with IPF demonstrate secondary pulmonary artery hypertension (PAH); it has been proposed that sildenafil, a treatment for PAH, may benefit patients by preventing increased pulmonary hypertension during physical activity, resulting in increased exercise tolerance and thereby quality of life.

Objective:

The objective of this selective EBM review is to determine whether or not sildenafil improves physical function in patients with idiopathic pulmonary fibrosis.

Methods:

The population studied was anyone with a diagnosis of idiopathic pulmonary fibrosis. The intervention used in these studies was oral sildenafil. The treatment groups were compared

to control groups who received a visually matched placebo in the RCTs. The primary outcome measured was improved physical function as demonstrated by increased distance on the 6-minute walk test when compared to a control group. The types of studies included two randomized, double blind, placebo controlled clinical trials and one open label study where all patients were given sildenafil, then separated into groups of responders or non-responders.

Key words in data searches included “Idiopathic pulmonary fibrosis” and “sildenafil”. All articles were published in the English language and appeared in peer reviewed journals between 2007 and 2010. The author researched articles via PubMed. The articles were selected based on relevance to clinical question and had to contain patient oriented outcomes (POEMs). Inclusion criteria used for selection was clinical trials, preferably randomized controlled trials. Studies were excluded if they were not studying idiopathic pulmonary fibrosis, sildenafil, or did not contain POEMs. Inclusion and exclusion criteria specific to each study is included in table 1. Two of the studies included dichotomous data; one of which used 90% confidence intervals (CI) and non-parametric bootstrap analysis; the other used 95% CI, Chi square, and presented CER, EER from which NNT, NNH, ABI, and ARI were calculated. The last study presented only continuous data utilizing a change in mean from baseline at 5% level of significance.

Table 1: Demographics of Included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Collard[1] (2007)	Open label study	14	72 ± 7	1.diagnosis of IPF 2. Diagnosis of Pulmonary Hypertension	1. Contraindications to use of Sildenafil	0	Sildenafil 20-50 mg TID
Idiopathic Pulmonary Fibrosis Clinical Research Network[2] (2010)	Double blind RCT	180	69.8 ± 8.7 (exp.) 68.2 ± 9.3 (control)	1. Diagnosis of IPF 2. In Advanced stage of the disease (CO diffusing capacity < 35% predicted)	1. 6-Minute walk distance (6MWD) < 50 m, 2. Diff. > 15% in (6MWD) between two prerandom. walks, 3. use of nitrates, 4. Aortic stenosis 5. pulmonary rehab 6. Tx with prostaglandins, endothelin-1 antag., or phosphodesterase inhibitors 7. resting O2 sat < 92% on 6 L of oxygen, 8. Being on a lung transplant list	5	Treatment regimen of Sildenafil 20mg TID
Jackson[3] (2010)	Double blind RCT	29	70 ± 12 (exp.) 71 ± 6 (control)	1. presentation of IPF within 3-36 mo before screening 2. Diagnosis of IPF using HRCT or VATS bx 3. PA_{sys} 25-50 mmHg and no R HF 4. 21-85 years old, 5. 6MWD >150/<500m, 6. Worsening in past yr, 7. ability to understand sign written consent 8. absence of other causes of UIP, CA, or infection 9. fvc 40-90%, dclo 30-90%	1. Severe Pulm. HTN, 2. severe HF (NYHA III or IV), 3. FEV1/FVC < 0.5 4. RV >120% pred. 6. any condition other than IPF likely resulting in death within 2 years 7. unstable/degenerative. cardiac/neuro. Disease 8. pregnancy/lact., 9. current tx with other IPF meds. 10. arthritis, CVA, or other limitation to mobility 11. O2 sat < 80% at rest 12. Cr > 1.5 x norm. 13. WBC <2,500; neut <1500; hct <30%, plt <100,000 14. billi> 2x norm., AST/ALT/alk. Phos. > 3 x norm, albumin < 3	4	Sildenafil 20 mg daily for 3 days, 20 mg twice daily for 3 days, and then 20 mg three times daily for the remainder of the trial

Outcomes Measured:

The primary outcome measured across all three studies was 6-minute walk distance (6 MWD) as assessed by 6-minute walk test (6 MWT) according to American thoracic society (ATS) protocol. 6 MWT were administered before starting treatment and again upon treatment completion (study end point). Additional outcomes were measured in the two RCT's. In the study by Idiopathic Pulmonary Fibrosis Clinical Research Network 2010, degree of dyspnea as measured by the University of California, San Diego, Shortness of Breath Questionnaire and the Borg Dyspnea Index. The shortness of breath questionnaire has patients rate 21 activities of daily living (ADLs) on a scale from 0-5, along with 3 ratings on limitations caused by dyspnea or fear of dyspnea, with a higher score equating to more severe dyspnea. The borg dyspnea scale measures perceived dyspnea on a scale from 0-10, 10 being the worst. In the study by Jackson et al. 2010, the additional outcome assessed dyspnea, measured using a borg scale.

Results:

All three of the studies reviewed utilized the intervention of oral sildenafil for the treatment of IPF, only two of which were RCTs. Of the two RCTs, only one presented its data in a dichotomous format, the other was presented in continuous format, which was not convertible to dichotomous. The open label study also presented its data in a dichotomous format; however, there was no comparison group. There was also some difference in length of the study, and dosage of sildenafil utilized.

In the Collard et al. 2007 study, sildenafil dosed between 20 and 50 mg TID was given, depending on the formulation available, and the 6 MWD was assessed before the study began and again after three months of treatment. The 14 patients were then dichotomized in to groups

of "responders" (≥ 20% change in 6 MWD, from before and after treatment) and "non-responders" (< 20% change in 6 MWD or unable to complete 6 MWT), 57% of patients (n=8) were classified as responders. The mean improvement in 6 MWD in patients who completed both 6 MWT (n=11) was 49 meters (within 90% CI based on nonparametric bootstrap estimates). This leaves 3 patients who were unable to complete the follow up 6 MWT; sildenafil was stopped in two patients because of adverse reactions (diarrhea, transient hypotension) and the third patient was unable to complete the walk test due to chest discomfort. It was reported that out of the 14 patients only one had serious adverse event (transient hypotension) related to the sildenafil.

The study by the Idiopathic Pulmonary Fibrosis Clinical Research Network 2010,was a RCT that enrolled 180 patients and assessed their 6 MWD before and again after 12 weeks of treatment with either sildenafil 20 mg or a visually matched placebo, given TID. A chi square was utilized to measure rates of improvement in the sildenafil and placebo groups. A positive response was defined as improvement of 20% or more on testing of the 6 MWD from baseline to 12 weeks in both groups. Patients were deemed to have no response if improvement was less than 20% at baseline, if they died, if they withdrew from the study, or had missing data. Treatment effect was summarized with 95% confidence intervals and a P value of 0.049 or less was required for statistical significance. In the sildenafil group 9 of 89 patients (EER 10%) had a positive response and 6 of 91 patients (CER 7%) in the placebo group had a positive response (P=0.39). Serious adverse events were 15% (EER) and 16% (CER) of patients in the sildenafil and placebo groups respectively (P=0.73). Tables 2 and 3 show calculated treatment effect values. Additionally, mortality in the sildenafil group was 2 patients and in the placebo group was 4 patients (P = 0.43). Dyspnea as measured by the shortness of breath questionnaire showed

scores remaining stable in the sildenafil group and worsened in the placebo group (estimated difference -6.58; P=0.006); and showed no significant difference in the borg scale.

Table 2: Efficacy

P-Value	**EER**	**CER**	**RBI**	**ABI**	**NNT**
0.39	10%	7%	42.85%	3%	34 for 12 weeks

Table 3: Safety

P-Value	**EER**	**CER**	**RRI**	**ARI**	**NNH**
0.73	15	16	-6.25%	-1%	-100 for 12 weeks

The Jackson et al. RCT enrolled 29 patients and slowly adjusted the dosage of sildenafil; 20 mg daily for 3 days, 20 mg twice daily for 3 days, and then 20 mg three times daily for the remainder of the trial, and assessed 6 MWD before treatment, at 3 months, and again at 6 months. It was stated that there was no significant difference between the placebo group (n=15) and sildenafil group (n=14) mean 6 MWD at 6 months. A change in mean from baseline at 5% statistical significance was used to evaluate this; Table 4. Also, there was no change in dyspnea as denoted by the mean borg score, after 6 months; table 5. There were 7 adverse events with 6 occurring in the sildenafil group and 1 occurring in the control group. No serious adverse events occurred and there were no mortalities during this study.

Table 4: Mean distance ± SD after 6 month (meters)

P-value	**Sildenafil**	**Placebo**
0.256	324 ± 41 m	355 ± 82 m

Table 5: Mean borg score ± SD after 6 month

P-value	Sildenafil	Placebo
0.492	4.1 ± 2.3	3.4 ± 1.6

Discussion:

Sildenafil was originally used to enhance penile erection, but has since been proven effective at reducing pulmonary vascular resistance and is therefore approved for use in idiopathic pulmonary arterial hypertension.[3] It is classified as a phsphodiesterase-5 inhibitor, and works by stabilizing cGMP thereby increasing nitric oxide causing vasodilation of pulmonary vasculature. This same mechanism was theorized to be effective in enhancing physical function in patients with IPF in all three of the reviewed studies.

These studies are difficult to compare to one another due to the variation in data evaluation and study type. Sildenafil appeared to be a promising treatment in patients with IPF from a purely physiologic and mechanistic standpoint. The data from the open label study weakly supported this idea, with the majority of their patients (57%) falling into a responder category. This study had a number of weaknesses from an evidence standpoint; there were no distance requirements for inclusion or exclusion in the study, the study was not a blinded RCT, and the variability of sildenafil dosing was wide (20mg-50mg TID).

The other two studies were double blind RCT's and that provided similar conclusions through different methods. The idiopathic pulmonary fibrosis clinical research network 2010

study showed that while sildenafil was relatively safe, NNH -100 for 12 weeks (P= 0.73), it was not shown to be especially efficacious when compared to the placebo group, NNT 34 for 12 weeks (P = 0.39). Some limitations, as assessed by the study itself are; findings only pertain to patients with advanced IPF (D_LCO <35%), treatment effect could have been driven a subgroup (ie. patients with severe PAH), and the study was too short and small to assess the duration of the effect of sildenafil or possible effect on acute exacerbation or death. The Jackson et al. 2010 study followed 29 patients for 6 months and found that there was no significant change from mean in either the sildenafil or placebo group. There were 7 adverse events, none of them serious, 6 of the events occurred in the sildenafil group. There were some limitations reported by this study. First, the minimum dose of sildenafil found effective in IPAH was used (20 mg TID) and this dose may not be effective in patients with IPF. Second, patients who had severe IPAH were excluded and this may have been a subgroup showing particular benefit.

Furthermore, differences in 6 MWD as inclusion criteria varies across all three studies. In the Collard et al. 2007 study there was no required baseline 6 MWD criteria. The study by idiopathic pulmonary fibrosis clinical research network 2010 required a minimum of 50 m. Lastly, the Jackson et al. 2010 study had even more rigid requirements, $\geq$ 150 m and $\leq$ 500 m. This variation could account for significant variation in results. However, the RCTs seem to have similar conclusions despite these differences.

A major limitation in my own methods was the fact that I only used PubMed as a source. I focused on the first three clinical trials I found; with two of them being RCTs. This review would have benefited by searching other literature databases such as EBSCO or CINHAL for a third RCT instead of a settling for an open label trial.

Conclusion:

After review of the three clinical trials, it appears that sildenafil does not improve physical function in patients with idiopathic pulmonary fibrosis. While the open label study highlights a possible correlation between the use of sildenafil and improved physical function, it is too weakly designed to be considered evidence and simply points to the need for further study. The two RCTs reviewed, which give the strongest evidence, utilize different methods of analysis for the data gathered but come to the same conclusion; there was no significant difference in response between sildenafil and placebo groups. While sildenafil does not appear to be especially effective at the given dosage, it was relatively safe across all 3 studies. Future studies could focus on an increased dose of sildenafil, as the dose studied was the minimally effective dose for treatment of patients with PAH. Also, inclusion criteria in regards to initial 6MWD could be lessened, allowing for more patient enrollment in future studies; and even a modest improvement at a lower distance could make a big change in quality of life. Lastly, studies into sildenafil's effect on dyspnea in patients with IPF could show benefit; based on secondary outcomes in two of the reviewed trials.

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